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A Review on the Potential Usage of Lionfishes (*Pterois spp.*) in Biomedical and Bioinspired Applications

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Abstract

Lionfishes are recognized as invasive and predatory species in the world. The genus *Pterois* belongs to the Scorpaenidae family has 10 confirmed species. Among them, two species *Pterois miles* and *P. volitans* were reported as non-indigenous species in Turkish marine waters. Although dorsal, pelvic, and anal fins of lionfish have venom-releasing spines which can have systemic effects such as severe pain, fever, vomiting, and dizziness, there are no reports of death by lionfish in the literature anyway. After careful removal of the venomous spines, lionfish meat is suitable for human consumption. The bioactivity of homogenates obtained from the venomous spines of lionfish has been the subject of various research since the 1950s. Until now, it has been proven that the venomous spines of the lionfish contain anticancer, antiviral, anti-inflammatory, anticoagulant, antioxidant, and antibacterial compounds and can be used in biomedical applications as a natural resource of marine origin. Moreover, the spine shape of lionfish has provided inspiration that can be useful in designing reusable syringe needles and sterilizable plungers, thereby reducing biomedical waste and sharps disposal costs. Additionally, the fins and spines of lionfish, which are typically removed and discarded, are used to make jewellery. This review, therefore, focused on evaluating alternative management actions to bring these invasive fish into the economy and control their populations, owing to both their use in biomedical fields and their suitability for bioinspiration.

Keywords:
Lionfish, venom, spine, bioactivity, bioinspiration

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Background

Venomous organisms are represented in many taxa, including kingdom Animalia. During evolution, animals have developed special organs for the production and injection of venoms (Mebs, 1994; Utkin, 2015). Venom is secreted from a special gland in animals that contains molecules that disrupt normal physiological processes when injected by the organism to kill prey and defend the organism against attacks by predators (Arbuckle, 2017; Gokulalakshmi et al., 2018; Schendel et al., 2019).

The enormous biomedical potential found in venoms of various species worldwide of terrestrial organisms have been deeply emphasized and well researched (Church & Hodgson, 2002; Ziegman & Alewood, 2015). However, the scientific gap regarding the biomedical potential of marine organisms is relatively large compared to terrestrial organisms, the most known and studied of which are snakes, scorpions, and spiders (Escoubas et al., 2000; Church & Hodgson, 2002; Terlau & Olivera, 2004; Koh et al., 2006; King, 2015; Lopes-Ferreira, 2014; Ortiz et al., 2015; Casewell et al., 2017; Jawad, 2018; Ashwood et al., 2020). This inconsistency can be explained by several reasons such as the marine organisms not having such a tremendous epidemiological threat, the extreme instability of the toxic components they contain, and the difficulties associated with the extraction, isolation, and storage of the venom (Campos et al., 2017; White & Meier, 2017).

Among the marine organisms, fish make up more than half of all venomous vertebrates (Nelson, 1984). Smith & Wheeler (2006) suggested in a phylogenetic analysis that up to 1200 fish in 12 clades should be considered venomous. The toxicity of these venomous fishes indicates potent physiological activity. Therefore, it is quite possible that toxic substances in piscine venom could yield valuable biomedical compounds (Sivan, 2011).

There are over 250 species of marine fish well-known or suspected to be poisonous, including lionfish, scorpionfish, butterflyfish, stonefish, weeverfish, toadfish, stargazers, and some species of sharks, stingrays, ratfish, eel catfish, surgeonfish, and blenny fish species (Smith & Wheeler 2006; Kiriake & Shiomi, 2011; Sivan, 2011).

The opening of the Suez Canal in November 1869 connected the tropical Red Sea with the Mediterranean, known for its primarily temperate fauna, dramatically affecting both marine commerce and the biodiversity of the Mediterranean (Turan et al., 2015; Doğdu et al., 2016; Stamouli et al., 2017; Turan et al., 2020). Lionfish are recognized as an invasive and predatory species in the world (Morris et al., 2009; Schofield, 2010; Johnston & Purkis, 2014; Poursanidis, 2015; Eagderi et al., 2019). The genus Pterois belongs to the Scorpaenidae family and has 10 confirmed species (Froese & Pauly, 2022), among them, *Pterois miles* and *P. volitans* are the most invasive (Morris et al., 2009; Schofield, 2010; Johnston & Purkis, 2014; Poursanidis, 2015). They entered the Eastern Mediterranean via Suez Canal (Bariche et al., 2017) and was firstly recorded from the Israeli coast (Golani & Sonin, 1992), then towards the north, Lebanon (Bariche et al., 2013) and Cyprus (Evripidou, 2013; Oray et al., 2015). In Turkish marine waters, *P. miles* was

firstly reported by Turan et al. (2014) from the Iskenderun Bay, and spreaded westward towards the Mersin (Yağlıoğlu & Ayas, 2016) and Antalya Bays (Özbek et al., 2017) and the Aegean coasts of Turkey (Turan & Öztürk 2015; Bilge et al., 2016; Turan et al., 2018; Özgül, 2020; Oruç et al., 2022). As for *P. volitans*, the first observation in the Mediterranean was reported by Gürlek et al. (2016) in the Iskenderun Bay and followed by Gökoğlu et al. (2017) from Antalya Bay, and Ayas et al. (2018) from Mersin Bay.

In the last decade, the lionfish has extended its range to the central Mediterranean and continues to expand into the western Mediterranean. Lionfish inhabit warm marine waters at depths from 1 to 300 feet on hard bottom, mud bottoms, mangroves, sea grasses and coral reefs (Albins & Hixon, 2008; Ferreira, 2015; Turan, 2020). They are opportunistic predators, consuming anything that fits in their mouths such as fishes, shrimps, and crabs (Albins & Hixon, 2008; Côté, et al., 2013; Andradi-Brown et al., 2017).

In addition, lionfish mature in less than a year can spawn year-round as often as every four days, and females can produce up to 40000 eggs per spawning event (Côté, et al., 2013). Their egg masses are encased in toxic mucus that prevents predation (Mulgrew, 2020). Lionfish have 18 venom-releasing spines linked with the dorsal, pelvic, and anal fins, thirteen of which are on the dorsal, three on the anal and two on the pelvic. Humans can fall victim to lionfish when fishermen, divers, and swimmers accidentally step on, handle, and have their skin pierced by the spines (Haddad Junior, 2021).

Lionfish venom includes acetylcholine and neurotoxin and can cause systemic effects such as severe pain, fever, vomiting, dizziness even cardiac arrhythmias and pulmonary edema (Hornbeak & Auerbach, 2017). However, there are no reports of death by lionfish injuries in the literature (Haddad et al., 2015a; Haddad et al., 2015b). After careful removal of the venomous spines, lionfish meat is suitable for human consumption (Haddad et al., 2015b). The bioactivity of homogenates obtained from the venomous spines of lionfish has been the subject of various research since the 1950s (Church & Hodgson, 2002).

Until now, it has been proven that the venomous spines of the lionfish contain anticancer, anticoagulant, antioxidant, antiviral, and antibacterial compounds and can be used in biomedical applications as a natural source of marine origin (Memar et al., 2016; Sayed et al., 2016; Sommeng et al., 2019a,b,c,d; Becerra-Amezcua et al., 2020; Sommeng et al., 2020a,b). Moreover, the shape of the spine of the lionfish provides inspiration that can be useful in designing reusable syringe needles and sterilizable plungers (Galloway & Porter, 2019), along with its typically removed and discarded fins and spines, which is also used to make jewellery (Kleitou et al., 2019), thereby reducing biomedical waste and sharps disposal costs. Therefore, this review focused on evaluating alternative management actions to bring these invasive fish into the economy and control their populations, owing to both their use in biomedical fields and their suitability for bioinspiration.

Extractions of Crude Venom From Spines

Considering that the venom gland of lionfish is not a well-defined structure, it is technically problematic to collect venom in an uncontaminated form. Therefore, to date, venom studies have been carried out using homogenates obtained from venomous spines of lionfish.

Memar et al. (2016) isolated the venom components of *Pterois russelli* sampled from the Persian Gulf, Iran. In the experiment, they powdered the spines in porcelain with liquid nitrogen. Then they homogenized the pieces in 10 volumes of 0.02 M ammonium acetate, incubated for 24 h, and centrifuged at 664 g for 15 min. Finally, the pellet was discarded, and the supernatant of crude venom lyophilized by a freeze dryer. Sayed et al. (2016) obtained venom homogenate from the spines of *P. miles* in the Red Sea. They firstly kept the dorsal spines of *P. miles* in 10% glycerol solution at -80°C. The frozen samples were thawed and ground in 10% glycerol using a chilled mortar and pestle. The resultant suspension was then centrifuged at 7000 g for 10 min. The pellet was re-suspended in 10% glycerol and re-centrifuged. Finally, they pooled the supernatants. Sommeng et al. (2019a,b,c) extracted the venom spine protein of *P. volitans* collected from the Java Sea, Indonesia using the method previously described by Savitri et al. (2012). They sonicated the spines twice each for 8 minutes at 20 kHz. The samples were centrifuged 2 times for 15 minutes at 4500 rpm. They heated the sample at 60°C, 75°C, and 90°C for 10 minutes to isolate the proteins in the crude venom. After heating, they centrifuged the sample at 15000 x g for 30 min. They added 90% ethanol and 20%, 40%, 60% and 80% saturations of ammonium sulfates to the obtained supernatants and re-centrifuged at 4500 rpm. Finally, they separated the supernatants containing the venom protein. Sommeng et al. (2019d) isolated venomous protein from *P. volitans* spines from the Java Sea, Indonesia. Firstly, they cut the spines into small pieces, added 0.01 M phosphate buffer solvent containing $CaCl_2$ 0.001 M to increase the solubility of the phospholipase A2 protein (Shiomi et al., 1998), and incubated for 24 hours at 4°C. After incubation, they used the above-mentioned processes in their previous studies (Sommeng et al., 2019a,b,c). Becerra-Amezcua et al. (2020) extracted venom from the spines of *P. volitans* collected from Mahahual coasts, Caribbean Sea. Initially, they removed the venomous dorsal spines and stored them in 10% glycerol solution at -80°C. The frozen samples were thawed and ground in 10% glycerol using a chilled mortar and pestle. The resultant suspension was then centrifuged at 4500 g for 10 min. The pellet was re-suspended in 10% glycerol and re-centrifuged. The supernatants were pooled.Sommeng et al. (2020a) performed venom extraction of *P. volitans* from Indonesian sea waters to isolate phospholipase A2. In this experiment, briefly, they firstly immersed 50 g of the spine in 0.01 M phosphate buffer and 0.1 M $CaCl_2$ for 8 min at 40°C. After preparation, they centrifuged the sample to separate the impurity residue from the crude venom at 15000 g for 30 min. The supernatant was heated in a water bath at 60°C for 30 min and then re-centrifuged at 15000 g for 30 min. They were added to the supernatant with 80% ammonium sulfate salt and centrifuged at 15000 g for 30 min. Finally, the precipitate was dissolved in 0.01 M phosphate buffer and CaCl2. Sommeng et al. (2020b) isolated the spine venom of *P. volitans* from Indonesian sea waters. They applied similar

protocols to their previous studies (Sommeng et al., 2019a,b,c). In this study, the only difference was that the final solution was centrifuged at 30000×g for 30 min.

Bioactivities of Venomous Spines

In recent years, many studies have been carried out on the bioactivity of the venomous spines of invasive lionfish species, which will pave the way for their use in biomedical applications.

Memar et al. (2016) studied the proteolytic, phospholipase, hemolytic, coagulation, edematogenic and dermonecrotic activities of *P. russelli* spine venom. They detected phospholipase A2 (PLA2) activity in the spine venom. Coagulation in human plasma was visualized after 7 and 14 seconds. They revealed that up to 30 mg showed proteolytic activity on casein. The highest edematic activity was detected at 20 mg 2 days after injection in Balb/c mice. Sayed et al. (2016) investigated the anticancer activity of *P. miles* venomous spines against human liver cancer cell line (HepG2) and found that crude venomous spine homogenate exhibited an anticancer effect on the HepG2 cancer cell lines up to very low concentrations reaching 7.5 µg/ml. Sommeng et al. (2019a) studied the antiviral activity of phospholipase A2 (PLA2) isolated from *P. volitans* spine venom on the human immunodeficiency virus. The authors reported that PLA2 from the venom showed strong inhibition on the SRV2-A549 cell lines. Sommeng et al. (2019b) investigated *P. volitans* spine venom extracts against cervical cancer cell line (HeLa) and found the highest percentage of inhibition in HeLa cells reach 17-19% at the highest dose of venom extract. Sommeng et al. (2019c) studied the antioxidant activity and bioactive components of *P. volitans* spine venom. They detected that the venom has weak antioxidant activity. As a result of Liquid Chromatography-Mass Spectrometer (LC-MS) analysis, the authors revealed several bioactive compounds Valine, L-arginine, Deanol aceglumate, Isatin, Hernandione, Sauvagnine, Hipppadine, Melanine and Cilostazol. Becerra-Amezcua et al. (2020) investigated the effects of *P. volitans* venom on brain functions. Zebrafish was used as a model organism in their study and the venom significantly affected the dopaminergic neurons and retarded embryonic development due to the venom also affects growth hormone secretion. The authors also concluded that lionfish venom should be further studied for its possible pharmaceutical effects on Alzheimers' disease. Sommeng et al. (2020a) determined that the coagulant activity of crude *P. volitans* spine venom can accelerate blood clot (procoagulant) up to 8.5 seconds. The LC-MS/MS analysis detected the procoagulant compound Nomega-nitro-L-arginine methyl ester (L-NAME). Sommeng et al. (2020b) examined the antibacterial activity of the phospholipase A2 (PLA2) enzyme of *P. volitans* spine venom against *Escherichia coli*, *Bacillus subtilis*, and *Staphylococcus aureus* using disc diffusion assay. They reported that the venom has antibacterial activity against S. aureus but does not affect the other bacteria.

Therefore, utilizing bioactive compounds from these venomous spines may be an alternative management strategy to conserve threatened biodiversity by suppressing populations in lionfish-invaded areas.

Bioinspiration from Spines and Fins

Until now, researchers studying the spinal mechanics of structures such as porcupine quill, cactus, and honeybee stings argue that spines can be inspired by the design of biomedical devices such as hypodermic needles (Cho et al., 2012; Bai et al., 2015; Sahlabadi et al., 2017). However, the lionfish spines are not hollow, serrated, or spiny, and instead release venom through grooves on the sides. Therefore, the lionfish spine design can be useful in creating reusable syringe needles and sterilizable plungers, which will reduce biomedical waste and insert disposal costs (Galloway & Porter, 2019). Jewellery made from the fins and spines of lionfish has been gaining in popularity day by day. Because of the venomous spines and unwanted fins, they are typically removed and discarded before the sale. These discards can be sold for use to make jewellery, which can increase the price of landed lionfish by up to 61% (Karp et al., 2015; Kleitou et al., 2019). Thus, the usage of spines and fins may be another possible strategy to prevent the invasion of lionfish owing to their suitability for bioinspiration.

In conclusion, lionfish can harm the ecosystem due to their opportunistic feeding preferences on native species. Unfortunately, there is a limited extermination pattern for this species yet. However, the spread of this species can be struggled by bringing it into the economy through alternative methods. In order for us to gain economic benefits from the lionfish, it is necessary to make people adopt that it is a very tasty fish and is safe for human consumption after its spines are removed. Small-scale fisheries combined with various incentives can be an effective and low-cost method of reducing lionfish on a spatial scale. Commercial, recreational and spear lionfish fisheries can be promoted to sustainably suppress populations in the long term. Increasing the use of bioactive substances obtained from lionfish in drug discovery studies with new perspectives and being inspired in the development of various biomedical products can be an effective strategy in preventing its spread by giving commercial importance to this species (Ulman et al., 2022). Consequently, further collaboration between biologists, engineers, pharmacologists, and medical doctors would be beneficial for developing biomedical and bioinspired applications and preventing their invasions.

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Author Contributions

The draft of the manuscript was written by A.U.

Conflict of Interest

The author declared that have no conflict of interest.

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